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The role of optical defocus in regulating refractive development in infant monkeys

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Abstract

Early in life, the two eyes of infant primates normally grow in a coordinated manner toward the ideal refractive state. We investigated the extent to which lens-induced changes in the effective focus of the eye affected refractive development in infant rhesus monkeys. The main finding was that spectacle lenses could predictably alter the growth of one or both eyes resulting in appropriate compensating refractive changes in both the hyperopic and myopic directions. Although the effective operating range of the emmetropization process in young monkeys is somewhat limited, the results demonstrate that emmetropization in this higher primate, as in a number of other species, is an active process that is regulated by optical defocus associated with the eye's effective refractive state. © 1999 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Emmetropization is the process that coordinates the growth of the eye's optical and axial components resulting in the development of a near emmetropic refractive error, typically a low degree of hyperopia. Although the exact nature of the mechanisms that are responsible for emmetropization is not well understood, several lines of evidence indicate that emmetropization is an active process that is regulated by visual feedback associated with optical defocus and the eye's effective refractive state (Wallman, 1993; Norton & Siegwart, 1995; Wildsoet, 1997; Smith, 1998).

Beginning with Wiesel and Raviola's (Wiesel & Raviola, 1977) report of extreme myopia in form-deprived monkeys, it has been consistently shown that procedures, which prevent the formation of a clear retinal image, disrupt emmetropization in a wide variety of animals including humans (Wallman, 1993; Smith, 1998). The myopia typically produced by form deprivation appears to be the result of unregulated axial growth associated with the absence of visual feedback concerning the eye's effective refractive state. These results emphasize that the potential for a clear retinal image is essential for normal emmetropization and indirectly suggest a role for the retinal image in the regulation of axial growth.

More direct evidence that visual feedback regulates ocular growth comes from the observations that restoring unrestricted vision in young animals with experimentally induced refractive errors promotes recovery (Wallman & Adams, 1987; Troilo & Wallman, 1991; Smith, Hung & Harwerth, 1994; Siegwart & Norton, 1998). For example, in chickens with form-deprivation myopia, restoring the potential for clear vision dramatically reduces axial growth rates, which if accompanied by the reduction in optical power that occurs during normal maturation, causes the eye to become less myopic (Troilo & Wallman, 1991).

Arguably the strongest evidence that emmetropization is regulated by visual feedback comes from studies in which the eye's effective refractive state was altered either optically with ophthalmic lenses (Schaeffel, Glasser & Howland, 1988) or by manipulating the visual environment (Miles & Wallman, 1990). Making the eyes of young chickens artificially myopic with positive spectacle lenses or hyperopic with negative spectacles produces a remarkable degree of compensating ocular growth (Schaeffel & Howland, 1988; Schaef-

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fel et al., 1988; Irving, Callender & Sivak, 1991; Irving, Sivak & Callender, 1992; Wildsoet & Wallman, 1995; Nevin, Schmid & Wildsoet, 1998). Young chick eyes can grow in a manner that will virtually eliminate imposed refractive errors produced by lens powers between about -10 and $+15$ D (Irving, Sivak & Callender, 1992; Wildsoet & Wallman, 1995).

To date, the evidence that optically induced changes in the eye's refractive state predictably influence the course of emmetropization in mammals, and particularly in higher primates, is limited. In young kittens, surgically induced hyperopia promotes the development of a relative myopia that appears to compensate for small degrees of surgically induced anisometropia (Hendrickson & Rosenblum, 1985). A stronger argument in favor of the visually guided growth hypothesis could be made if kittens also developed hyperopia in response to myopic defocus. However, in kittens and tree shrews, both positive and negative defocusing lenses either failed to alter refractive development (Nathan, Crewther, Crewther & Kiely, 1984) or, like form deprivation, resulted in relative axial myopia (Smith, Maguire & Watson, 1980; Ni & Smith, 1989; Siegwart & Norton, 1993).

Early studies of the effects of various lens-rearing regimens on refractive development in primates showed that optically simulating an anisometropia in infant monkeys disrupted emmetropization and the normal balance between the two eyes. However, the observed refractive changes were generally insufficient in magnitude (Smith, Harwerth & Crawford, 1985) and frequently in the wrong direction to compensate for the optically imposed errors (Crewther, Nathan, Kiely, Brennan & Crewther, 1988; Chung, 1993; Smith, Hung & Harwerth, 1994). However, the negative results obtained in these early studies can be attributed primarily to methodological issues. Specifically, the use of contact lenses, which has subsequently been shown to produce refractive alterations in infant monkeys via non-visual mechanisms, probably confounded many of these studies (Hung & Smith, 1996).

More recent experiments have shown that young marmosets (Judge & Graham, 1995) and infant rhesus monkeys (Hung, Crawford & Smith, 1995) exhibit differential interocular growth that predictably compensates for anisometropic spectacle lenses. However the magnitude of the interocular refractive-error compensation was limited (about 3 D) in comparison to that found in sub-primate species like the chicken. Thus, it appears that the effective operating range of the emmetropization mechanism is much smaller in primates. The smaller emmetropization range observed in primates could be due to a number of possible factors. For example, whereas chickens can exhibit substantial degrees of anisometropic accommodation (Schaeffel et al., 1988), accommodation is yoked in monkeys (Jampel, 1959; Jampel & Mindel, 1967). The large unilateral defocus that occurs with strong anisometropic lenses in primates could mask the sign of defocus or initiate visual system changes (e.g. amblyopia) that may somehow interfere with the normal emmetropization process (Kiorpes & Wallman, 1995).

The purpose of this investigation was to determine the extent to which lens-induced changes in the eye's refractive status could predictably alter ocular growth and the normal emmetropization process in infant macaque monkeys. In essence, our goal was to characterize the optical performance properties of the monkey's emmetropization mechanism. Some of these results have been presented briefly elsewhere (Hung et al., 1995; Hung, Huang & Smith, 1996; Smith, Hung & Huang, 1997).

2. Methods

2.1. Subjects

Rhesus monkeys (*Macaca mulatta*) were selected as subjects because the resulting data can be applied to human refractive development with a high degree of confidence. The animals were obtained at 1–3 weeks of age and were housed in our primate nursery that was maintained on a 12-h light/12-h dark lighting cycle. Initially, the infants were hand-fed infant formula by bottle five to six times per day. The number of daily bottle feedings was gradually reduced and solid foods gradually introduced until the animals were able to feed independently (about 4 months of age). Between 2 and 4 weeks of age, the experimental subjects were fit with lightweight helmets (Smith et al., 1985; Crawford, 1996) that held 25-mm diameter spectacle lenses in front of each eye at about a 7 mm vertex distance. Except for brief periods needed for routine cleaning and maintenance, the monkeys wore the helmets continuously for periods ranging between 10 and 23 weeks. The helmets were inspected at approximately 2-h intervals throughout the day to ensure that the helmets fit the subjects appropriately and that the spectacle lenses were clean and free of debris that might have interfered with the desired optical effects.

2.1.1. Controls

Data on normal refractive development were obtained from five infant monkeys that were reared with unrestricted vision. As a control for the helmet rearing procedures, two additional infants were fit with helmets that held zero-powered lenses in front of both eyes. Data for one of these control subjects were presented previously in Hung et al. (1995). Additional comparison data were obtained from the non-deviating eyes of 12 infants that had their fellow eyes surgically deviated

to produce esotropia at either 3 or 6 weeks of age. Although refractive development is not totally independent in the two eyes of infants (Hung et al., 1995; Wildsoet & Wallman, 1995), it is unlikely that the induced esotropia significantly altered emmetropization in the non-deviating eyes, since the refractive errors in the two eyes of these animals were typically well matched.

Control data were also available from a number of other normal monkeys that were used in unrelated studies. Data from 30 animals that were obtained when they were adolescents or young adults (≥ 2 years of age) provided an indication of the prevalence and interocular variability of refractive errors in normal adult monkeys. Data from an additional 63 normal 2- to 4-week-old animals that were not directly involved in this study helped to define the distribution of refractive errors for normal infants at ages corresponding to the onset of our lens-rearing regimen.

2.1.2. Optically induced anisometropia

An anisometropia was optically simulated in ten infants by securing a zero-powered lens over one eye and either a negative (-3 or -6 D) or positive spectacle lens ($+3$ or $+6$ D) over the fellow eye. Since infant monkeys typically have very similar refractive errors in their two eyes, this lens-rearing procedure altered the refractive balance between the two eyes by an amount equal to the power of the treatment lens. However, regardless of whether an animal wore positive or negative lenses over the 'treated' eye, this rearing strategy produced chronic, hyperopic defocus in one eye. Videoretinoscopy (see below) revealed that the infants reared with these anisometropic lenses adopted fixation patterns that minimized the amount of accommodative effort required to obtain clear vision. So for example, infants treated with negative lenses fixated with, and postured their accommodation for, the eyes viewing through the zero-powered lenses. Consequently, the secondary focal point for the eye viewing through the negative lens would always be effectively behind the retina for all viewing distances. On the other hand, the infant monkeys treated with positive lenses preferred to fixate with the eye viewing through the positive lens. As a result, the eye viewing through the zero-powered lens experienced hyperopic defocus. The results for this subject group were described briefly in a previous report (Hung et al., 1995) and in order to provide a more complete description of primate emmetropization are included in more detail in this paper. The goal of this anisometropia rearing strategy was to determine the effective 'isometropization' range for infant monkeys, i.e. what is the largest anisometropia that can be effectively eliminated by the emmetropization process.

To further investigate the possible range of anisometropic compensation, we reared four infant monkeys using an anisometropic lens strategy similar to that described by Judge and Graham (1995). These monkeys were initially fitted with helmets that held a positive lens over one eye and a plano lens over the fellow eye. To encourage the animals to actively fixate with each eye, each eye was alternately occluded with black tape for half the daily light cycle, with the occluding tape being switched mid-way through the light cycle. Over the course of the rearing period, the power of the positive lens was increased in small increments in an effort to promote greater anisometropic compensation. In some cases the zero-powered lens was also replaced with a negative lens, again in an effort to promote higher degrees of anisometropic compensation. By encouraging the animals to actively fixate with each eye, this rearing strategy had two potential benefits. First, it reduced the likelihood that the rearing procedures would result in other visual system alterations, such as amblyopia, which may have somehow interfered with compensating ocular growth (Kiorpes & Wallman, 1995). Another benefit is that, by ensuring that each eye actively fixates through its treatment lens, it was possible to independently shift each eye's effective refractive state in either a myopic or hyperopic direction.

2.1.3. Binocular alterations in effective refractive error

In general, the above anisometropic strategies are useful because interocular comparisons can provide a very sensitive reference for any treatment-related alterations in refractive development. However, even though abnormal visual experience can produce substantial interocular differences in refractive error (Raviola & Wiesel, 1985), the emmetropization process in the two eyes of young animals may not be totally independent (Hung et al., 1995; Wildsoet & Wallman, 1995). To avoid confounding influences associated with potential interocular interactions, symmetrical, binocular alterations in effective refractive error were produced by rearing infant monkeys with equal-powered lenses over both eyes. With this rearing strategy, it was also possible to simulate both absolute myopic and absolute hyperopic refractive errors.

A total of 17 infants were reared with equal, fixed-powered lenses over both eyes. Within this group of animals, the lens powers varied from -6 to $+12$ D. The goal of this experiment was to determine the effective operating range of the emmetropization process in normal infant monkeys, i.e. the range of initial refractive errors that would eventually lead to emmetropia.

To help determine the extent to which spectacle lenses can alter refractive development, eight additional infants were also treated with equal-powered binocular

lenses. But for these animals, the powers of the lenses were increased in a progressive manner during the treatment period. For animals treated with positive lenses, the initial lens powers were matched to the animals' natural refractive error and subsequently increased as the eyes compensated for the lenses. Negative-lens-treated monkeys were started with plano powered lenses and subsequently the lens power was increased in the minus direction in attempts to maintain an imposed hyperopic error of at least 3–4 D.

All of the rearing and experimental procedures were reviewed and approved by The University of Houston's Institutional Animal Care and Use Committee and were in compliance the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Optical and biometric measurements

The subject's refractive errors, corneal curvatures, and their eyes' axial dimensions were measured at the start of lens wear and periodically throughout the treatment and subsequent recovery periods. To make these measurements, the monkeys were anesthetized (ketamine hydrochloride, 15–20 mg/kg and acepromazine maleate, 0.15–0.2 mg/kg, i.m.; topical corneal anesthesia, one to two drops of 0.5% tetracaine hydrochloride) and cycloplegia was induced by the topical application of two drops of 1% tropicamide. Although tropicamide is not as effective as some agents in producing cycloplegia in primates, the absolute differences between the effects of tropicamide and other cycloplegic agents are small and predictable (Lovasik, 1986; Mutti, Zadnik, Egashira, Kish, Twelker & Adams, 1994) and the use of tropicamide has several advantages in longitudinal studies. The effects of tropicamide are very repeatable (Mutti et al., 1994) and, in comparison to more potent drugs, tropicamide is faster acting and has a much shorter duration of action (Marron, 1940; Lovasik, 1986). Since even small interruptions in special rearing procedures can have dramatic effects on refractive development (Napper, Brennan, Barrington, Squires, Vessey & Vingrys, 1995; Schmid & Wildsoet, 1996), it was important to minimize the duration of cycloplegia because multiple measures were made during the lens-rearing period. Moreover, stronger drugs, like atropine, have been shown to directly influence ocular growth via their direct action on the retina or sclera (Stone, Lin & Laties, 1991; McBrien, Moghaddam & Reeder, 1993; Wildsoet, McBrien & Clark, 1994; Kaymak, Hagel & Schaeffel, 1997). Thus, stronger cycloplegic agents would be more likely to confound the effects of visual experience.

During a given session, the eyes' refractive errors were measured independently by two investigators using a streak retinoscope and hand-held trial lenses. A given eye's refractive status was specified as the mean, spherical-equivalent, spectacle-plane, refractive correction of these two measures. For many animals, refractive status was also measured with a hand-held, auto-refractor (Retinomax, Nikon). The auto-refractor, which provided a magnified view of the subject's eye, was aligned on the pupillary axis. The retinoscopy and auto-refractor measurements were well correlated (Fig. 1). The retinoscopy measurements were, however, on average 0.8 D less myopic or more hyperopic than those obtained with the auto-refractor which can probably be attributed to criterion differences and possible differences in the ocular structures that reflect visible versus infrared light (i.e. the 'small eye' artifact of retinoscopy) (Glickstein & Millodot, 1970). The departure of the best fitting regression line in Fig. 1 from a slope of 1.0 reflects the fact that the autorefractor's assumed vertex distance was about 4–6 mm closer to the eye than the position of the hand-held lenses employed in retinoscopy.

The refracting power of the cornea was determined with a hand-held keratometer (Alcon Auto-keratometer). Three measurements were obtained when the reflected mires of the keratometer were positioned symmetrically around the eye's pupillary axis, which could be easily identified in the magnified view provided by the instrument. The mean corneal power, based on an assumed refractive index of 1.3375, was calculated from the matrix representations of the three readings (Keating, 1983; Harris, 1988). Some younger monkeys had corneas with refracting powers that exceeded the measurement range of the keratometer (> 62.0 D). In those cases, a video-topographer (EyeSys 2000), which was also aligned on the pupillary axis, was employed to

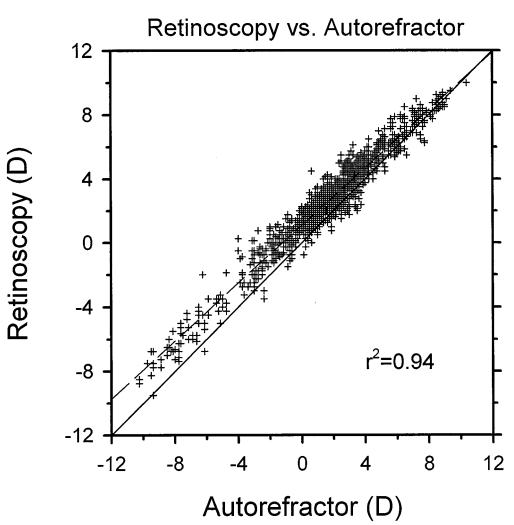

Fig. 1. Spherical-equivalent, spectacle-plane refractive corrections for the right eyes of normal and experimental subjects obtained by retinoscopy versus those measured with the automated optometer. Data are shown for both observers. The dashed line represents the best fitting straight line (slope = 0.90, $r^2 = 0.94$).

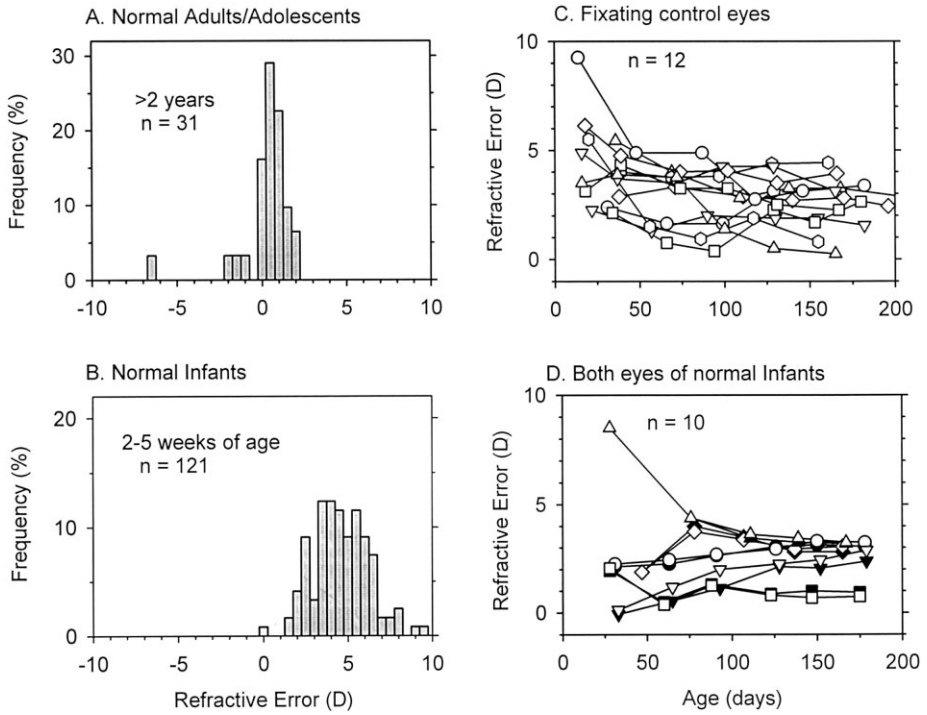

Fig. 2. Frequency distributions of the spherical-equivalent refractive errors for the right eyes of normal monkeys that were older than 2 years of age (A) and for those of normal infant monkeys ($n = 121$) 2–5 weeks of age (B). Spherical-equivalent refractive errors plotted as a function of age for the fixating, control eyes of 12 monkeys that had the fellow eye surgically misaligned before 6 weeks of age (C) and for both eyes of five infant monkeys that were reared with normal visual experience (D).

measure refracting power at the corneal eccentricities normally sampled with a keratometer.

Axial dimensions were measured by A-scan ultrasonography. In the initial stages of this study, the eye's overall axial length was obtained using an instrument with a 10 MHz, focused transducer (Sonometric Digital Biometric Ruler). The mean of at least five separate placements of the probe was used to represent the eye's axial length. The great majority of data were obtained with an instrument (Mentor Image 2000, 7 MHz transducer) that provided information on individual ocular components, in particular vitreous chamber depth. This instrument provided the average of ten separate measures. Both instruments employed a weighted average velocity of 1550 m/s to calculate intraocular distances.

2.3. Fixation pattern

For animals reared with anisometropic lenses and for binocularly treated animals that developed an anisometropia, the eye the animal preferred to fixate with and the effective sign of defocus were determined by infrared videoretinoscopy performed at several fixation distances (Schaeffel, Farkas & Howland, 1987). Beginning 1 or 2 days after the onset of lens wear, video images were recorded with the camera positioned at an 82-cm working distance and with the animal viewing through the treatment lenses. Data were collected for several levels of accommodation by attracting the animal's attention to toys held at 10, 82 cm and 3.2 m. The amount and sign of defocus relative to the camera was determined for each eye by measuring the relative height of the retinoscopic reflex (Howland, 1985). The eye that showed the smallest amount of defocus for the fixation target was considered to be the fixating eye.

3. Results

3.1. Normal refractive development

Fig. 2A and B show refractive-error distributions for 30 normal monkeys that were 2 years of age or older and for 121 infants that were 2- to 5-weeks-old, respectively. In comparison to the older monkeys, our infant monkeys were more hyperopic (median = +4.4 D vs. +0.5 D; mean = +4.4 D vs. +0.22 D) by an amount that greatly exceeded any potential small-eye artifacts associated with retinoscopy (about +0.5 D for infant vs. adult monkeys) (Glickstein & Millodot, 1970). Overall, refractive status was also more variable in our infant population and the distribution of refractive errors exhibited a much lower degree of kurtosis than that for the adult population (kurtosis: +0.26 vs. +12.60).

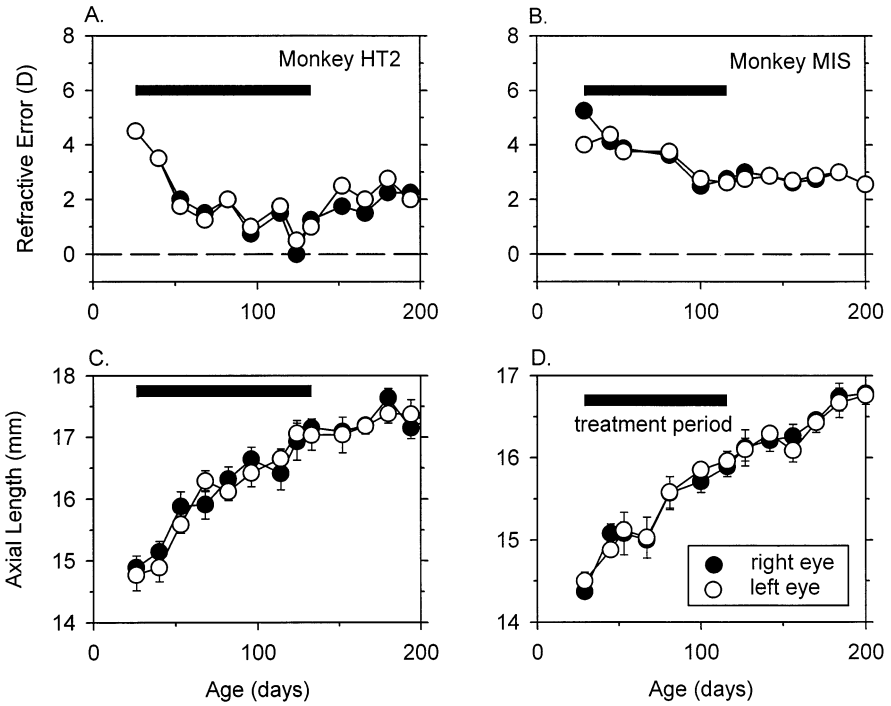

Fig. 3. Spherical-equivalent refractive errors (A and B) and axial lengths (mean ± S.D.; C and D) plotted as a function of age for the right (filled) and left eyes (open) of two control monkeys reared with plano lenses in front of both eyes. The filled horizontal bars represent the periods of time that the monkeys wore the treatment lenses.

As illustrated in Fig. 2C and D, much of the emmetropization process that eliminates the differences between these two refractive-error distributions takes place within the first 3–5 months of life. In panel C, refractive error is plotted as a function of age for the fixating, non-deviating eyes of the 12 infant monkeys that had the fellow eye surgically deviated to produce an esotropia at either 3 or 6 weeks of age. Panel D shows refractive-error data for both eyes of the five normally reared infants. For both groups of monkeys, refractive error converges rapidly to a moderate degree of hyperopia. By 6 months, the average refractive error was $+2.6 \pm 1.1$ D with a median value of 2.8 D. During this rapid phase of emmetropization, most eyes exhibited a systematic reduction in hyperopia. However, many animals which were initially less hyperopic exhibited either little change in refractive error or showed relative hyperopic shifts toward these moderate levels of hyperopia. It is also important to note that in the five normal infants (D), the refractive-error changes were well coordinated in the two eyes. Despite substantial changes in overall refractive error, no anisometropia over 0.87 D was observed.

Zero-powered lenses did not alter refractive development. Fig. 3 illustrates the refractive errors and axial lengths for the left and right eyes of the two infant monkeys that were reared with zero-powered lenses over both eyes. Both infants had substantial hyperopic errors at the start of lens wear. During the early period of rapid axial elongation, both infants exhibited systematic reductions in hyperopia so that by the end of the treatment period (indicated by the filled horizontal bars), they showed the moderate degrees of hyperopia that are typical of normal infant monkeys. Although monkey MIS had a 1.5 D anisometropia at the onset of lens wear, the anisometropia quickly disappeared. Thereafter, the refractive errors and axial dimensions for the left and right eyes of both control monkeys were well matched during and after the lens-rearing period.

3.2. Optically induced anisometropia

As illustrated in Figs. 4 and 6, low-powered, anisometropic spectacles predictably disrupted the normally coordinated growth between the two eyes of infant monkeys. For monkeys treated with either $+3$ or -3 D lenses, the non-fixating eyes experienced hyperopic defocus at the start of the treatment period (i.e. the eyes viewing through the zero-powered lenses for the monkeys treated with $+3$ D anisometropic spectacles and the -3 D eyes for the subjects wearing -3 D anisometropic lenses). Relative to the fixating eyes, the defocused eyes exhibited faster growth rates during lens wear and developed more myopic or less hyperopic refractive errors. For the four infants shown in Fig. 3, the direction and magnitude of the anisometropia was sufficient to compensate for the treatment lenses. The fact that the degree of anisometropia

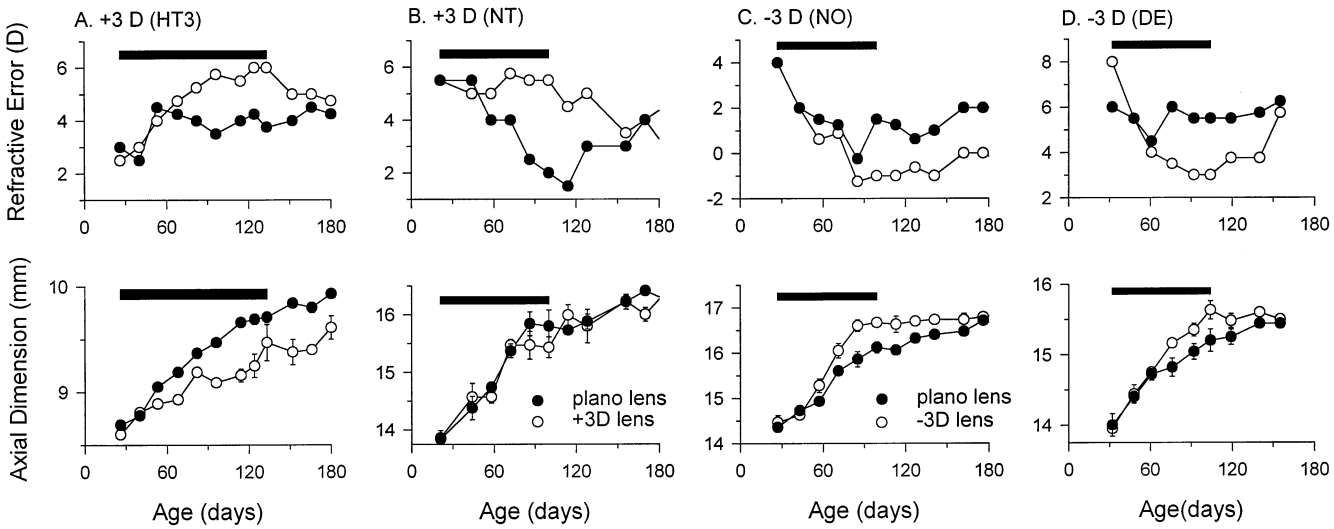

Fig. 4. Spherical-equivalent refractive error (top) and either vitreous chamber depth (mean ± S.D.; bottom left) or axial length (bottom three right panels) plotted as a function of age for representative monkeys reared with + 3.0 D (A and B) or − 3.0 D lenses (C and D) in front of their treated eyes (open symbols). The fellow eyes viewed through zero-powered lenses (filled symbols). The filled horizontal bars indicate the lens-treatment periods.

appeared to stabilize before the end of the treatment period supports the idea that the refractive changes had adequately compensated for the lenses. Consequently, by the end of the treatment period, both eyes of these four monkeys were simultaneously in focus when the animals viewed through the anisometropic lenses.

Not all of the monkeys treated with 3 D anisometropic lenses exhibited complete compensating anisometropic growth. The third monkey treated with a − 3 D lens developed a 1.5 D anisometropia that partially compensated for the treatment lens, however, the third monkey treated with a + 3 D lens remained essentially isometropic (Fig. 6).

The growth pattern exhibited by the fixating eyes of the monkeys treated with + 3 D lenses provided additional evidence that the anisometropic lenses altered emmetropization. In contrast to normal emmetropization, the fixating eyes of all of the monkeys treated with + 3 D lenses (i.e. the eyes viewing through the + 3 D lenses) either maintained their initial degree of hyperopia (Fig. 4B) or showed absolute hyperopic shifts during the treatment period (Fig. 4A). Thus, when these animals viewed through their treatment lenses, they effectively experienced a moderate degree of hyperopia that was comparable to the refractive errors of normal monkeys at 5–6 months of age. In agreement with the idea that the relatively high degrees of hyperopia attained by these eyes represented compensating growth, all of the eyes treated with + 3 D lenses exhibited systematic reductions in hyperopia following lens removal.

None of the infants treated with 6 D anisometropic lenses exhibited convincing evidence of compensating interocular growth (Fig. 5). Monkey ME (Fig. 5A) initially appeared to show compensating growth. Shortly after the onset of lens wear, ME exhibited large systematic differences in refractive error. However, at about 60 days of age, this animal switched its fixation preference from the eye viewing through the + 6 D lens to the eye viewing through the zero-powered lens. Subsequently, there was a systematic reduction in anisometropia to near zero. In general, the monkeys treated with 6 D lenses showed interocular differences in refractive error that were greater than those observed in control animals (Fig. 6). Although these anisometropias were in the appropriate direction to compensate for the treatment lenses, the interocular differences were typically smaller than those produced by 3 D anisometropic lenses and they were clearly not large enough to compensate for the 6 D lenses.

3.3. Anisometropic spectacles and alternating occlusion

By alternately patching each eye for half the daily light cycle, and thus actively encouraging the infant monkeys to fixate with each eye, it was possible to produce larger degrees of compensating growth with anisometropic spectacles. Fig. 7 illustrates refractive development and vitreous chamber growth for two monkeys that developed substantial anisometropias. Because these animals also developed substantial degrees of astigmatism, particularly in the eyes that viewed through the positive lenses, refractive status is represented in two ways. The smaller symbols show the spherical-equivalent refractive errors. The larger symbols represent the most hyperopic and most myopic meridians for the eyes treated with positive (filled symbols) and negative lenses (open symbols), respectively.

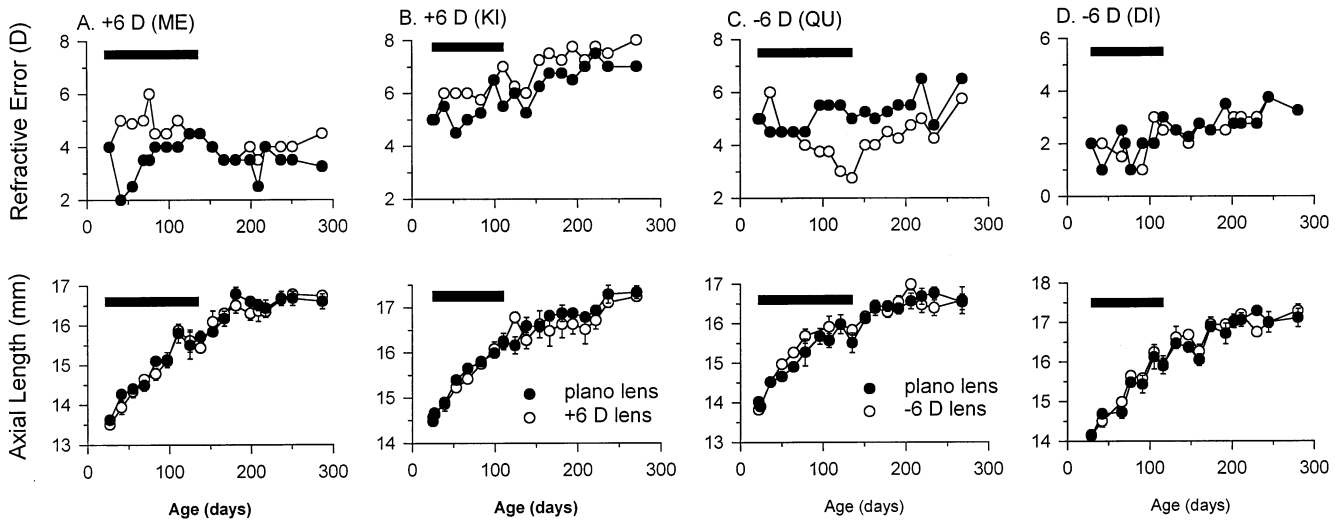

Fig. 5. Spherical-equivalent refractive error (top) and axial length (mean ± S.D.; bottom) plotted as a function of age for representative monkeys reared with +6.0 D (A and B) or −6.0 D lenses (C and D) in front of their treated eyes (open symbols). The fellow eyes viewed through zero-powered lenses (filled symbols). The filled horizontal bars indicate the lens-treatment periods.

The differences between the corresponding small and large symbols represent half of an eye's astigmatism. While the spherical equivalent data provide a useful reference, for eyes with substantial amounts of astigmatism, specifying the refractive correction for the most ametropic meridian is more appropriate. Astigmatic infants appear to posture their accommodation for the secondary focal point for one the principal meridians rather than the circle of least confusion (i.e. the dioptric position associated with the spherical equivalent ametropia). Specifically, videoretinoscopy revealed that infant monkeys with large degrees of astigmatism typically postured their accommodation for the least hyperopic or most myopic meridians rather than the circle of least confusion. In agreement with this observation, in monkeys reared with cylindrical lenses, emmetropization appeared to be directed toward the line foci for one of the principal meridians, typically the least hyperopic meridian, rather than the circle of least confusion (Smith, Huang & Hung, 1997).

During the first 60 days of lens wear, Monkey EL (Fig. 7A) developed 4.5 D of compensating anisometropia in response to 7.5 D of optically induced anisometropia. A further +1.5 D increase in positive power for the right lens at 84 days of age failed to produce an additional increase in anisometropia. Instead, Monkeys EL showed a relatively constant 4.5 D of anisometropia until the lenses were removed. Monkey KO (Fig. 7B) exhibited a larger amount of compensating anisometropic growth. Over the first 75 days of lens wear, Monkey KO developed 6.5 D of anisometropia in response to 6.5 D of optically induced anisometropia. A further increase in lens powers did not produce any additional compensating anisometropia. However, the time-locked reduction in anisometropia that occurred in response to the small reductions in lens powers that were begun at day 111 indicates that KO's anisometropia developed in response to the interocular differences in refractive error produced by the treatment lenses.

Panels C and D demonstrate that the anisometropias in Monkeys EL and KO animals were associated with substantial interocular differences in vitreous chamber growth rates. The interocular differences in refractive astigmatism were also associated with differences in corneal astigmatism (Fig. 7E, F). In each eye, the corneal astigmatism closely matched the direction and magnitude of refractive astigmatism.

3.4. Binocular alterations in effective refractive error

Symmetrical binocular alterations in refractive error were employed to investigate the effective operating range of the emmetropization process in infant monkeys. Lens powers that simulated large hyperopic errors produced an interesting range of responses. As shown in Fig. 8, which illustrates data for the four monkeys treated with −6 D lenses, some monkeys were able to compensate for large degrees of hyperopia. For example, monkey IVA (Fig. 8A) exhibited 5 D of hyperopia at the start of the treatment period. The −6 D treatment lenses effectively increased the degree of hyperopia to 11 D. During the course of lens wear, both eyes developed 5 D of absolute myopia, an overall myopic shift of 10 D. Consequently, at the end of the treatment period, when this animal was looking through the −6 D lenses, he manifested a low degree of hyperopia. Monkey ZA (Fig. 8B), which experienced 8 D of effective hyperopia at the start of lens wear, showed evidence of compensating growth in one eye. Shortly after

the onset of lens wear, ZA showed a 3 D myopic shift in both eyes. Subsequently, ZA's left eye developed a sufficient degree of myopia to fully compensate for the treatment lens, however, the right eye stabilized at about 1 D of myopia. Following the onset of the anisometropia, videoretinoscopy indicated that ZA fixated with his left eye. As a result, the right eye experienced increasing amounts of hyperopic defocus for the remainder of the treatment period.

Other animals treated with −6 D lenses showed limited or no evidence for compensating growth. Monkey SNA (Fig. 8C), who experienced the largest effective hyperopia (13.25 D), showed a 5 D reduction in hyperopia during the first 100 days of lens wear. However, an additional 30 days of lens wear failed to produce a further reduction in the remaining 8 D of effective hyperopia. Monkey ROS (Fig. 8D), despite experiencing over 10 D of effective hyperopia, showed essentially stable refractive errors in both eyes throughout the treatment period. Although young monkeys have very large amplitudes of accommodation (Bito, DeRousseau, Kaufman & Bito, 1982; Smith & Harwerth, 1984), videoretinoscopy indicated that neither monkey SNA or ROS routinely accommodated to overcome their residual hyperopia, instead both animals habitually experienced a relatively high degree of hyperopic defocus.

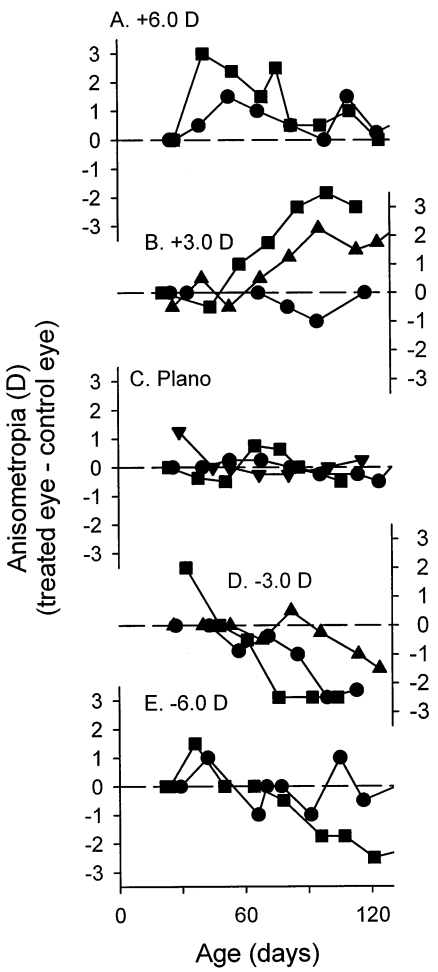

Fig. 6. Interocular differences in spherical-equivalent refractive error plotted as a function of age for individual monkeys reared with anisometropic spectacle lenses. Negative values indicate that the treated eye was more myopic or less hyperopic than the fellow eye that viewed through zero-powered lenses. The powers of the anisometropic lenses are indicated for each graph. Control monkeys were reared with zero-powered lenses in front of both eyes (panel C). All data were obtained during the treatment period. The first point for each subject indicates the start of lens wear.

Infants treated with either bilateral +3 or −3 D lenses consistently compensated for the experimentally induced changes in effective refractive error. For example, monkey QUA (Fig. 9A) initially experienced 7 D of effective hyperopia through −3 D treatment lenses. During the lens-rearing period, the refractive errors of both eyes shifted in the myopic direction by 6 D. At the end of the treatment period, QUA's refractive errors had stabilized at −2 D which resulted in an effective hyperopic error of 1 D. Monkey NOR (Fig. 9C) also showed initial myopic changes in both eyes following the application of −3 D lenses. However, NOR's left eye stabilized near +2.5 D, while the fellow eye continued to change in the myopic direction. The refractive error of the right eye, which videoretinoscopy confirmed was the fixating eye, stabilized near −1 D resulting in an effective refractive error of about +2 D when the right eye fixated through the −3 D lens.

Whereas −3 D lenses exaggerated the normal reduction in hyperopia during emmetropization, +3 D lenses consistently reduced the absolute changes that occurred during early refractive development. For example, both monkeys RO and SA (Fig. 9B, D) were moderately hyperopic at the start of lens wear. However, in contrast to normal animals or animals reared with −3 D lenses, neither animal showed a substantial reduction in hyperopia while wearing the +3 D lenses. RO exhibited an initial decrease from +5.50 D to around +4.0 D during the first 2–4 weeks of lens wear, but thereafter the refractions of both eyes remained relatively stable for the rest of the treatment period. Monkey SA showed virtually no change in refraction during the treatment period. As a result SA's effective refractive status produced by viewing through the +3 D lenses was between about +1 and +2 D throughout the treatment period. One interpretation of this development pattern is that there was little need for emmetropization in these monkeys because the spectacle lenses artificially produced emmetropia. The argument is bolstered by the observation that these animals invariably showed clear signs of emmetropization following removal of the treatment lenses. As illustrated in Fig. 9B and D, both monkeys RO and SA showed approximately 2 D drops in hyperopia immediately after the lenses were removed. Eventually their refractive errors stabilized between +2 and +3 D.

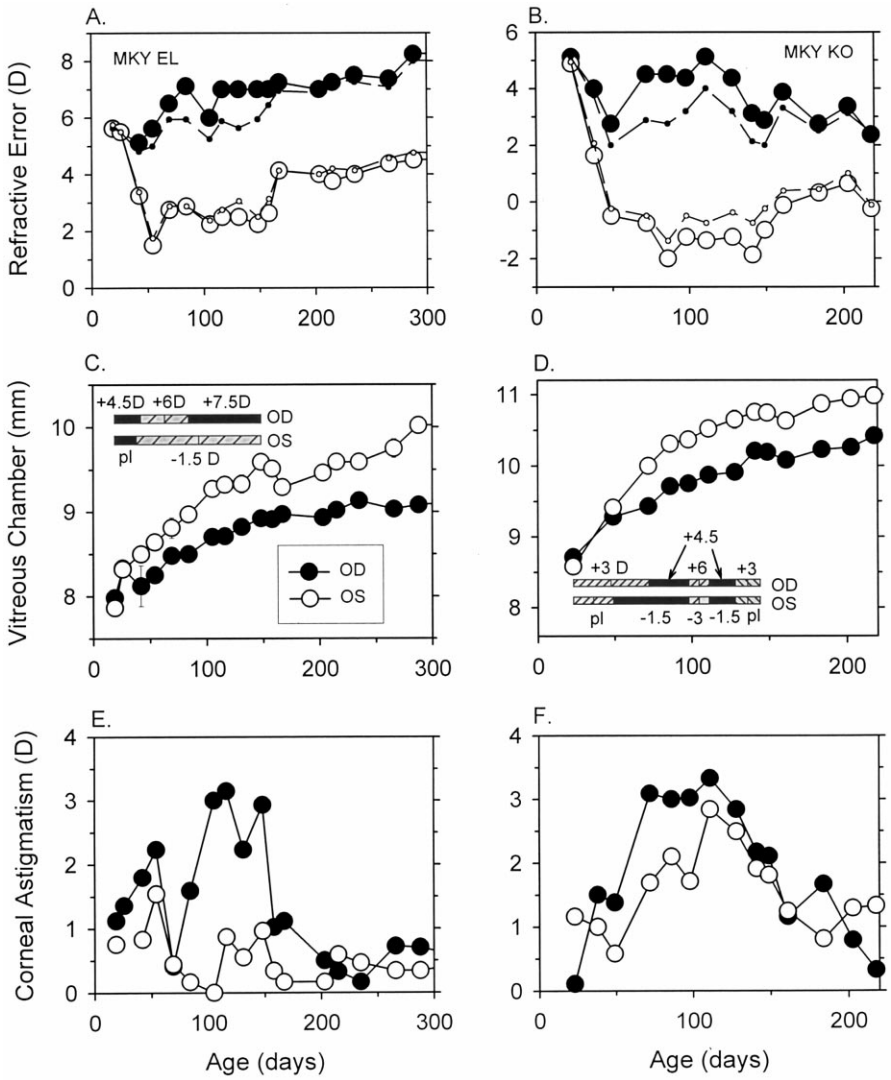

Fig. 7. Refractive error (A and B), vitreous chamber depth (mean ± S.D.; C and D), and corneal astigmatism (E and F) plotted as a function of age for the right (filled) and left eyes (open) of two monkeys reared with anisometropic spectacles. To ensure that the animals actively fixated with each eye, each eye was alternately occluded with black tape for half the daily light cycle. The powers of the lenses are indicated above or below the horizontal bars that indicate the lens treatment sequence for each eye. In A and B, the larger filled symbols represent the refractive corrections for the most hyperopic meridians for the positive-lens-treated eyes; the larger open symbols represent the most myopic meridians for the negative-lens-treated eyes. The smaller symbols represent the spherical-equivalent refractive errors.

The higher-powered positive lenses ($+6$, $+9$ or $+12$ D) virtually eliminated the reduction in hyperopia normally associated with emmetropization (Fig. 10). Like most normal infants, the monkeys treated with high-powered positive lenses were moderately hyperopic at the start of lens wear, but unlike most normal infants, all of the treated animals showed either stable refractive errors during lens wear or they exhibited modest hyperopic changes. It should be noted that this general pattern of refractive development was very similar in all animals reared with high-powered positive lenses, regardless of magnitude of the effective refractive error produced by the treatment lenses. For example, the $+6$ D lenses that were fitted to monkeys WI and NI (Fig. 10A, D) closely matched their initial refractive errors. Consequently, when viewing through the treatment lenses these animals were essentially emmetropic and presumably in terms of refractive-error development, emmetropization was largely complete. It is reasonable to argue that the relatively stable refractive errors shown by monkeys WI and NI represent compensation for the treatment lenses. The progressive decline in hyperopia exhibited by these subjects following lens removal is in agreement with this idea. However, none the animals treated with $+9$ or $+12$ D lenses exhibited refractive changes that fully compensated for the treatment lenses (at least when refractive error is specified for an infinitely distant fixation point). In every case, the $+9$ and $+12$ D lenses exceeded the subject's initial refractive errors and, thus, effectively

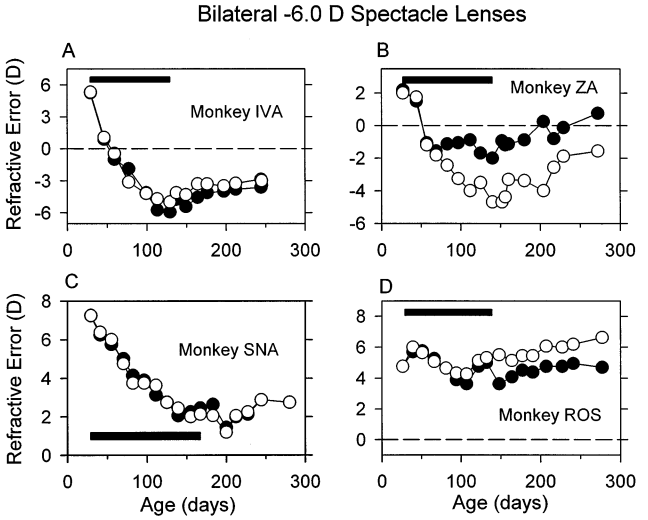

Fig. 8. Spherical-equivalent refractive error plotted as a function of age for the right (filled) and left eyes (open) of four monkeys reared with −6.0 D spectacle lenses over both eyes. The filled horizontal bars represent the lens-rearing period.

simulated a myopic refractive error (Fig. 10B, C, E, F). However, in no instance did a treated monkey exhibit an absolute hyperopic shift that was large enough to eliminate these effective myopic errors. Instead, the monkeys' refractive errors were relatively stable for the duration of lens wear. But, as observed in animals treated with lower-powered positive lenses, following lens removal all animals showed a time-locked reduction in hyperopia down to expected levels.

It is also noteworthy that the refractive errors for the two eyes of the animals treated with positive lenses, regardless of lens power, were typically well matched.

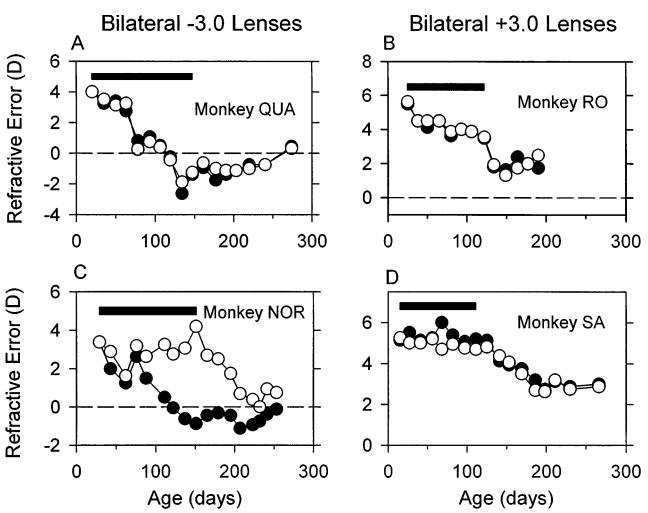

Fig. 9. Spherical-equivalent refractive error plotted as a function of age for the right (filled) and left eyes (open) of representative monkeys reared with either +3.0 D (B and D) or −3.0 D spectacle lenses over both eyes (A and C). The filled horizontal bars represent the lens-rearing period.

None of the positive-lens-reared monkeys developed anisometropias during the treatment period that were comparable to those exhibited by some of the monkeys treated with negative lenses.

The alterations in refractive development produced by binocular, equal-powered lenses were associated with changes in the rate of vitreous chamber elongation. Fig. 11A shows relative vitreous chamber depth plotted as a function of age for individual monkeys. The open symbols represent data for the three subjects reared with −3 D lenses and the two monkeys reared with −6 D lenses that showed compensating refractive growth (subjects ZA and IVA). The filled symbols represent the positive-lens-reared monkeys in Figs. 9 and 10. Overall, the negative-lens-reared monkeys exhibited much faster vitreous chamber growth rates than the positive-lens-reared monkeys. On average, the increase in vitreous chamber depth over the first 3 months of the treatment period was more than twice as large for animals reared with negative lenses (mean = 1.82 ± 0.45 mm) than it was for the positive-lens-reared monkeys (mean = 0.83 ± 0.2 mm).

The recovery that was observed in many lens-reared monkeys following lens removal was also mediated predominately by variations in vitreous chamber growth (Fig. 11B). In monkeys that developed myopia during the treatment period (open symbols), vitreous chamber growth virtually came to a halt immediately upon providing unrestricted vision. The refractive errors of these monkeys then shifted in the hyperopic direction as the cornea (and possibly the lens) continued to flatten and decrease in refracting power. In comparison, eyes that compensated for positive lenses (filled symbols) exhibited continued vitreous chamber growth during the recovery period that outpaced the changes in corneal power resulting in relative myopic shifts.

Fig. 12A summarizes the refractive errors of the fixating eyes at the end of the treatment period for all of the monkeys that were reared with bilateral equal-powered lenses. The animals treated with the higher powered lenses, particularly the positive lenses, typically exhibited a moderate degree of hyperopia which, as shown in Figs. 8–10, came about because the refractive errors of these animals were relatively stable throughout the treatment period. Thus, with the higher-powered lenses, refractive error was not correlated with lens power. However, refractive error was highly correlated with lens power for lens powers between −3 and +6 D ($r^2 = 0.80$). The main point is that moderate powered lenses predictably altered the eye's refractive status.

Fig. 12B demonstrates that the emmetropization process in infant monkeys has a limited effective operating range. For refractive errors between about −2 D of myopia and +8 D of hyperopia, the changes in refrac-

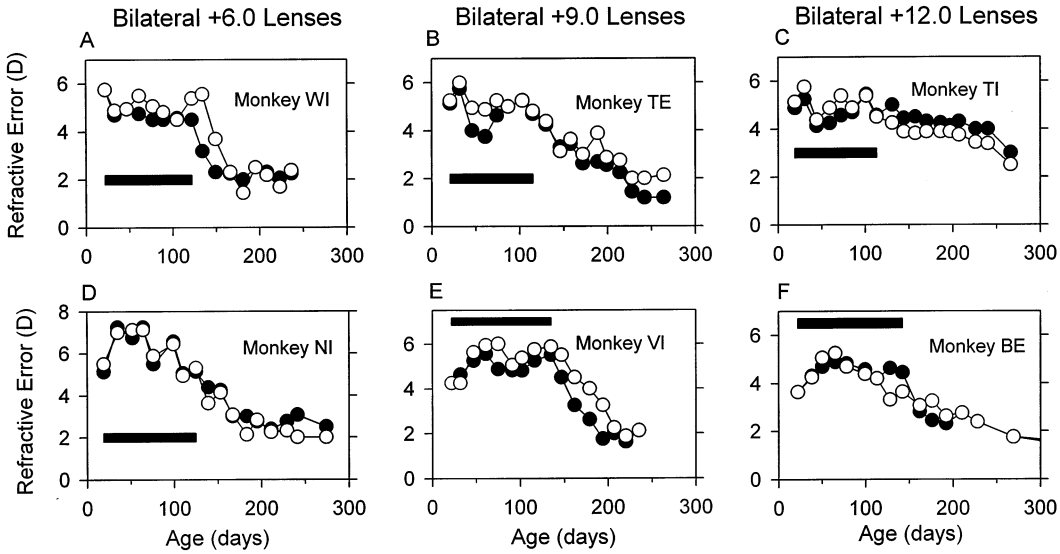

Fig. 10. Spherical-equivalent refractive error plotted as a function of age for the right (filled) and left eyes (open) of representative monkeys reared with either +6.0 D (A and D), +9.0 D (B and E), or +12.0 D spectacle lenses over both eyes (C and F). The filled horizontal bars represent the lens-rearing period.

tive error during early development were significantly correlated with the initial effective refractive error. Within this range, infant monkey eyes can grow in a manner that compensates for the refractive error so that by about 4–5 months of age, the eye will attain a low degree of hyperopia. Regression analysis of the data within this range demonstrates that the best fitting straight line has a slope of −0.78 and a r^2 value of 0.76. However, data for animals with initial refractive errors that fell outside this range clearly deviate from this line, particularly for the monkeys with the larger imposed myopic errors. For errors beyond −2 or +8 D, the emmetropization process either does not function or it is unable to produce changes in refractive error that are large enough to overcome the initial error.

To determine if it was possible to produce more substantial hyperopic shifts, we adopted a rearing strategy in which we attempted to impose a small, but constant, relative myopic error. Accordingly, the infants were first fit with equal-powered binocular lenses that largely corrected their natural refractive errors. Since infant monkeys typically grow toward low degrees of hyperopia, it was expected that the infants would exhibit a hyperopic shift to compensate for the treatment lenses. Animals corrected in this manner demonstrated an initial hyperopic shift of about 1–2 D following the onset of lens wear (Fig. 13). Subsequently, in response to changes in the animal's refractive status, the powers of the treatment lenses were increased in steps of 1.5 D in efforts to maintain a relatively constant stimulus for hyperopic growth. As shown in Fig. 13, this sequential lens strategy produced substantial hyperopic shifts. Monkeys CH and DI exhibited step-like increases in hyperopia that in many cases were clearly synchronized with changes in lens power. Over the course of the treatment period, the lens powers for these two monkeys were increased from +3 and +4.5 to +9.0 D. In response to the treatment regimen, both CH and DI developed an additional +4.5 D of hyperopia in their most ametropic meridians. Similar results were obtained with a third monkey that showed a hyperopic shift from +3.5 to +6.5 D in response to a final lens power of +7.5 D. However, the fourth monkey treated using this sequential positive lens strategy failed to become more hyperopic. Instead this fourth animal maintained a +4.0 hyperopic error throughout the treatment period.

In an analogous fashion, monkeys reared using a sequential negative-lens strategy exhibited systematic myopic shifts in refractive error. These animals were initially fit with zero-powered lenses. When the animals' refractive error either stabilized or reached a low degree of hyperopia, the powers of the lenses were changed to −1.5 D. Subsequently, the negative power of the lenses was increased in −1.5 D steps in efforts to maintain a stimulus for myopic growth. As illustrated in Fig. 14, this sequential negative-lens strategy resulted in systematic changes in refractive error in the myopic direction. For the four monkeys treated in this manner, the total treatment-related changes in refractive error ranged from 3.9 to 7.12 D. During the course of lens wear, one the these monkeys developed 2.6 D of anisometropia (not shown). As observed in other monkeys treated with negative lenses (e.g. Figs. 8 and 9), the anisometropia developed because the non-fixating eye stabilized at a relatively high degree of hyperopia while the fixating eye continued to undergo relative myopic changes in refractive error.

The refractive-error changes produced by the sequential lens-rearing strategies were also associated with alterations in vitreous chamber growth rates. The ordinate scales in panels C and D of Figs. 13 and 14 encompass the same range of vitreous chamber depths. A comparison of the slopes of the vitreous chamber versus age functions for the negative- and positive-lens-reared monkeys provides a clear indication of the nature of the induced refractive errors. For example, during the lens-rearing period, the vitreous chambers in positive-lens-reared monkeys CH and DI grew an average of 0.54 ± 0.33 mm. Over a comparable period, the vitreous chambers of negative-lens monkeys DE and BA increased by an average of 1.48 ± 0.06 mm. For the three monkeys that showed absolute hyperopic shifts, the vitreous chamber grew at an average rate of 5.61 ± 2.39 microns/day. In contrast, the average rate of vitreous-chamber elongation for the monkeys treated with sequential negative lenses was 12.24 ± 0.98 microns/day.

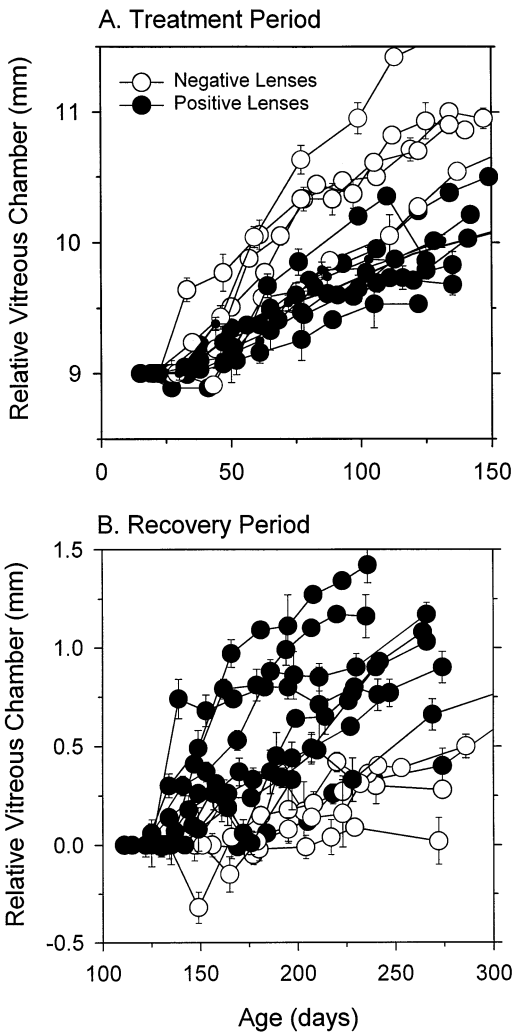

Fig. 11. (A) Relative vitreous chamber depth (mm) plotted as a function of age for representative monkeys reared with equal-powered, binocular lenses. The initial data point for each animal was normalized to 9.0 mm. All of the data were obtained during the treatment period. (B) The relative change in vitreous chamber depth (mm) that occurred following lens removal. In both plots, the open symbols represent the right or fixating eyes (for animals that also developed anisometropia) of the three monkeys that were reared with -3.0 D lenses and the two monkeys that exhibited compensating growth in response to -6 D lenses. The filled symbols represent the right eyes for all of the positive-lens-reared monkeys that are represented in Figs. 9 and 10.

Interestingly, a comparison of their spherical-equivalent refractive errors (small symbols in Fig. 13A, B) with the refractive errors for their most ametropic meridians (large symbols) shows that the sequential positive-lens strategy also resulted in a substantial degree of astigmatism. Keratometry showed that the refractive astigmatism closely matched the magnitude and axis of corneal astigmatism. Following lens removal and the return of unrestricted vision, there was a systematic reduction in both corneal and refractive astigmatism. The astigmatism produced by our lens rearing strategies will be addressed in detail in a subsequent paper, but it is important to note that the presence of astigmatism was not simply associated with our helmet rearing technique. As shown in Fig. 14 (and Fig. 7), eyes that are undergoing relative myopic changes rarely exhibit astigmatism.

4. Discussion

The emmetropization process directs the eyes of normal infant monkeys to grow in a coordinated and systematic manner toward a low degree of hyperopia, the 'desired' refractive state for young monkeys. The main finding of this study was that spectacle lenses could predictably modify the growth of one or both eyes and consequently alter an infant monkey's absolute refractive status and/or the refractive-error balance between its two eyes. Overall, these results provide strong support for the idea that emmetropization in higher primates is an active process that is regulated by optical defocus associated with an eye's effective refractive state. Moreover, throughout early primate development, visual feedback must be monitored in a relatively continuous fashion because removal of the treatment lenses after an infant's refractive status has stabilized or sequentially changing lens powers during the treatment period produces time-locked, compensating refractive-error alterations.

4.1. The operating characteristics of emmetropization in monkeys

For 2- to 4-week-old monkeys, the emmetropization process operates effectively for initial refractive errors between about -2 D of myopia to $+8$ D of hyper-

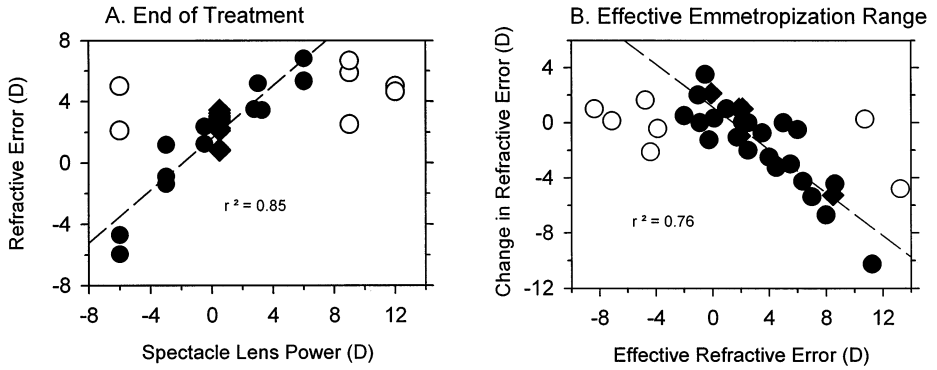

Fig. 12. (A) Spherical-equivalent refractive errors obtained at the end of the lens-rearing period for the right or fixating eyes of individual binocularly treated animals plotted as a function of the power of the treatment lenses. (B) The change in the spherical-equivalent refractive error that took place during the treatment period plotted as a function of the effective refractive error produced by viewing through the treatment lens at the start of the lens-rearing period. Data are shown for the right or fixating eyes of individual monocularly and binocularly treated monkeys. The filled diamonds represent normal monkeys. The filled circles represent monkeys that exhibited compensating growth, i.e. their final effective refractive error while viewing through the treatment lenses was emmetropia or a low degree of hyperopia. The open symbols represent monkeys that failed to compensate for the treatment lenses. The dashed lines represent the best fitting straight lines for the filled symbols (A, slope = 0.85, $r^2 = 0.85$; B, slope = -0.78; $r^2 = 0.76$).

opia. It is not surprising that the refractive errors of the great majority of normal infant monkeys fall within this range. In our sample of 121 normal infants, all but two monkeys showed natural refractive errors that fell within these limits. Both of the outlying monkeys had large hyperopic errors ($+8.5$ and $+9.25$ D); no infant had a myopic error that was larger than -2 D.

The operational limits of the emmetropization process do not simply reflect a physiological limit in the ability of the eye to change in response to visual feedback, particularly in the case of myopic defocus. Rather, with myopic defocus, it is likely that the relatively small range of compensation that was observed in response to high plus lenses was influenced by adaptive behavior in our infant monkeys and the manner in which we specified an animal's effective refractive status. In accordance with standard practice, our infant's effective refractive errors were referenced to optical infinity. However, many critical aspects of the visual worlds of our infant monkeys were located at much shorter viewing distances. The arms of an infant monkey are only about 10 cm long and much of their time is spent examining items that are typically within arms reach (e.g. their feeding bottles, toys, and other infants). The myopia imposed by high plus lenses would greatly reduce the accommodative demand for near objects. Accordingly, it is reasonable to speculate that our failure to observe larger absolute hyperopic shifts in response to large initial amounts of induced myopia was due in part to the fact that the monkeys habitually fixated near targets. In this scenario, instead of a consistent signal directing the eyes to grow in a more hyperopic direction, the treatment lenses would provide clear vision at the habitual near viewing distances and thus there would be little need for further changes in refractive error, i.e. emmetropization would be complete. Presumably it was possible to produce larger absolute hyperopic changes using our sequential lens regimen because the infants' refractive errors were effectively near emmetropia throughout much of the treatment period and they spent more time fixating distance objects.

The limited ability of infants to consistently compensate for imposed hyperopic errors over 8 D can not, however, be attributed to inconsistent visual feedback. Adaptive fixation strategies would not eliminate the error signal in this case and videoretinoscopy indicated that the animals that failed to compensate for large hyperopic errors did not overcome the imposed errors via accommodation. In fact just the opposite was observed. The eyes that failed to compensate for large negative lenses, both anisometropic and equal-powered binocular lenses, appeared to exhibit no effort to accommodate for the imposed error. As a result, these eyes chronically experienced a high degree of hyperopic defocus. It is possible that this chronic defocus initiated other visual system alterations that somehow interfered with emmetropization. Amblyopia appears to influence late refractive development in monkeys (Kiorpes & Wallman, 1995). Based on previous psychophysical investigations (Smith et al., 1985; Harwerth, Smith, Paul, Crawford & von Noorden, 1991), it is likely that the animals that failed to compensate for the imposed hyperopic errors developed amblyopia in their defocus eyes. The fact that forced alternating fixation increased the degree of anisometropia that could be produced by optical defocus suggests that infant monkeys must actively use their eyes in order for emmetropization to proceed normally. Judge and Graham (1995) drew a similar conclusion based on comparable results from

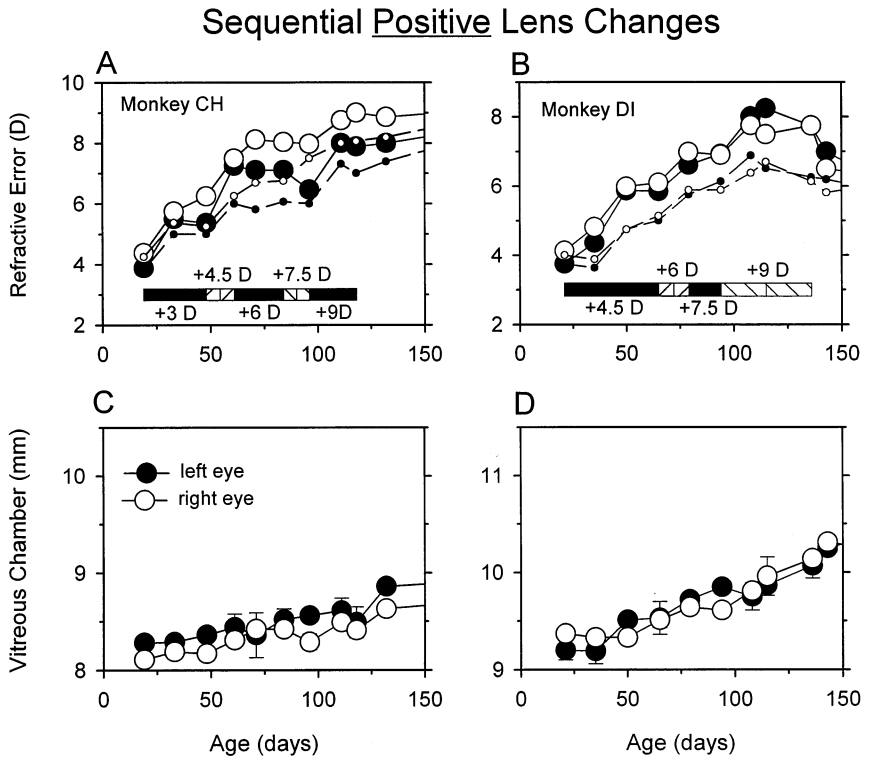

Fig. 13. Refractive error (A–B) and vitreous chamber depth (mean ± S.D.; C and D) plotted as a function of age for the right (open) and left eyes (filled) of two binocularly treated monkeys reared with sequential positive-powered lenses. The powers of the lenses are indicated above or below the horizontal bars that indicate the lens treatment sequence for both eyes. In A and B, the larger symbols represent the refractive corrections for the most hyperopic meridians; the smaller symbols represent the spherical-equivalent refractive errors.

the marmoset. Active fixation would certainly reduce the chances that a monkey would develop amblyopia. Regardless of what aspect of active usage is critical, it seems clear that factors other than just the quality or nature of the retinal image influence ocular growth.

It is interesting to note that the failure to actively fixate with an eye and the presence of amblyopia do not prevent form-deprivation myopia. Early form deprivation results in profound degrees of amblyopia and substantially higher relative myopic shifts than those observed in lens-reared monkeys (Harwerth, Smith, Boltz, Crawford & von Noorden, 1981; Raviola & Wiesel, 1985; Smith, Harwerth, Crawford & von Noorden, 1987). These form-deprivation results do, however, rule out the possibility that the hyperopic defocus limit in normal emmetropization is simply due to a physiological constraint associated with the maximum rate of axial elongation.

4.2. Ocular mechanisms responsible for lens compensation

Many aspects of primate emmetropization, lens-induced refractive compensation, and the recovery from experimentally induced errors can be attributed to a relatively simple mechanism that regulates vitreous chamber growth rate on the basis of the clarity of the retinal image. According to this idea which has been postulated by a number of investigators (Bartmann & Schaeffel, 1994; Wallman, 1993; Hung et al., 1995; Norton & Siegwart, 1995; Nevin et al., 1998), conditions that result in a blurred retinal image accelerate axial growth and promote myopia. On the other hand, conditions that produce clear images slow down vitreous chamber elongation, which potentially produces hyperopic shifts. It is assumed that the maturation of the cornea and lens and the concomitant decline in refracting power are relatively unaffected by changes in vitreous chamber growth rates.

Implicit in this model is the idea that accommodation requires effort and that animals with substantial degrees of hyperopia, either natural hyperopic errors or those imposed by negative lenses, do not always exert sufficient accommodative effort to fully compensate for their refractive errors. As a result, in comparison to infants with more ideal refractive states, these hyperopic monkeys would experience on a time-averaged basis a higher degree of defocus, which would result in a relative increase in vitreous chamber growth rate. As the degree of hyperopia declined, less accommodative effort would be required and these monkeys would experience longer periods with clear retinal images and show a concomitant reduction in axial growth. Presumably, once an infant's eyes reached the 'ideal' re-

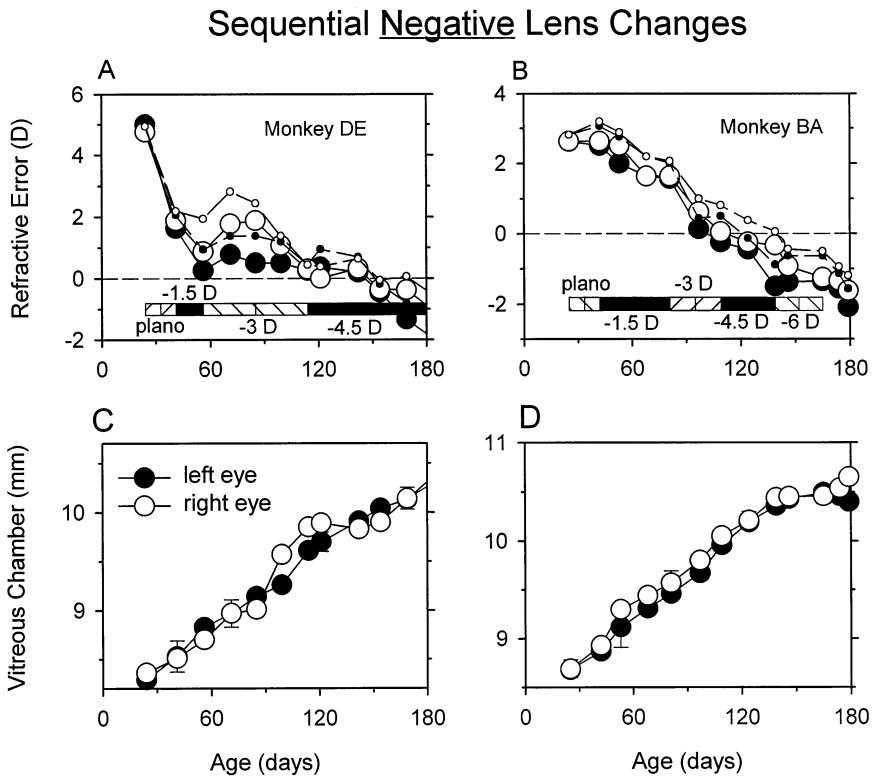

Fig. 14. Refractive error (A and B) and vitreous chamber depth (mean ± S.D.; C and D) plotted as a function of age for the right (open) and left eyes (filled) of two binocularly treated monkeys reared with sequential negative-powered lenses. The powers of the lenses are indicated above or below the horizontal bars that indicate the lens treatment sequence for both eyes. In A and B, the larger symbols represent the refractive corrections for the most myopic meridians; the smaller symbols represent the spherical-equivalent refractive errors.

fractive state, the time-average increase in retinal image clarity would be sufficient to essentially stop axial elongation. Further increases in axial length would then occur in concert with any further maturational reductions in corneal and lens power.

Positive lenses would stabilize hyperopic errors in infant monkeys by reducing the accommodative effort required to achieve a clear retinal image. Thus in comparison to uncorrected hyperopic monkeys, positive-lens-reared monkeys would experience longer periods in which the retinal image was in focus and a slow down in vitreous chamber elongation. Likewise recovery would occur in infants with experimentally induced myopia because, upon restoration of unrestricted vision, they would experience clear retinal images a greater proportion of the day than normal hyperopic infants would. Absolute increases in hyperopia would then result if vitreous chamber growth was slowed to the point that the normal ongoing reduction in refracting power out paced the vitreous chamber elongation.

In this emmetropization scenario, axial growth rate could be regulated by the same mechanisms that are responsible for form deprivation myopia (Raviola & Wiesel, 1985; Smith et al., 1987). Initial experiments in which infant monkeys were reared with diffuser contact lenses suggested that the degree of form deprivation that was required to produce exaggerated axial elongation was so high that it was unlikely that form-deprivation mechanisms would be activated by low to moderate degrees of optical defocus (Bradley, Fernandes, Tigges & Boothe, 1996). However, it is likely that non-visual factors associated with the use of contact lenses confounded the effects of optical diffusion in these experiments (Hung & Smith, 1996). In comparison, infant monkeys reared with diffuser spectacle lenses consistently develop axial myopia in response to amounts of optical diffusion that produce reductions in image contrast comparable to those associated with small amounts of optical defocus (Smith & Hung, 1995). These results suggest that form-deprivation mechanisms are probably sensitive enough to come into play during normal viewing conditions. The minimum amount of defocus that is required to produce axial elongation in infant monkeys is not known. In the chicken, Schmid and Wildsoet (1996) have recently reported that focusing errors that are comparable in magnitude to the estimated depth of focus of the chick eye are capable altering emmetropization. They also pointed out the intriguing possibility that the depth of focus for the emmetropization mechanism could be smaller than that for the perception of blur.

Although form deprivation mechanisms can feasibly account for many aspects of the compensating responses of primates to spectacle lenses, a single form-deprivation mechanism can not explain all our findings. For example, several eyes that experienced large amounts of hyperopic defocus failed to undergo emmetropization and instead remained relatively hyperopic. The above form-deprivation model would predict that these animals should have developed large axial myopias. A large body of research in the chicken suggests that multiple mechanisms influence early ocular growth and specifically that form deprivation myopia, the compensation for negative lenses, and the changes induced by positive lenses are not mediated by identical mechanisms (Troilo & Wallman, 1991; Bartmann, Schaeffel, Hagel & Zrenner, 1994; Schaeffel, Hagel, Bartmann, Kohler & Zrenner, 1994; Schaeffel, Bartmann, Hagel & Zrenner, 1995; Wildsoet & Wallman, 1995; Schmid & Wildsoet, 1996). In addition, many experiments support the hypothesis that there are growth-regulating mechanisms within the chick retina that can distinguish myopic from hyperopic defocus (Schaeffel, Troilo, Wallman & Howland, 1990; Diether & Schaeffel, 1997; Feldkaemper, Diether, Schwahn & Schaeffel, 1997; McClean & Wallman, 1997). At the present time, it is not known whether comparable mechanisms exist in the primate, however, as noted above, the mechanisms in the monkey that are responsible for lens compensation, unlike the mechanisms responsible for form deprivation myopia, appear to be influenced by factors associated with the development of vision disorders like amblyopia. Thus, it is appears that the monkey eye has multiple vision-dependent mechanisms that influence eye growth. If these multiple mechanisms are qualitatively similar to those in the chick, their presence could also account for the compensating growth produced by our lens-rearing procedures.

4.3. Comparisons between monkeys and chickens

From an operational point of view, the lens-induced compensation found in infant monkeys is qualitatively similar to that reported for the chicken, the most widely used animal in studies of refractive development. In both species, relative hyperopic and myopic changes that primarily reflect alterations in vitreous chamber growth rates occur in response to positive and negative lenses, respectively. When expressed in diopters, the effective operating ranges and gains of the mechanisms responsible for lens-induced compensation are lower in the monkey, as are the operating characteristics of the emmetropization mechanism in other mammalian species (marmoset, Judge & Graham, 1995; tree shrew, Siegwart & Norton, 1993). For example, for initial binocular errors between -2 D and $+8$ D, the gain of the emmetropization mechanism in infant monkeys is 0.78, i.e. a -3 D lens produces on average a relative myopic shift of about 2.3 D. In contrast, emmetropization in chicks exhibits a gain of 0.97 for anisometropic lens powers between -10 D and $+15$ D, i.e. a $+10$ D lens produces a relative hyperopic shift of 9.7 D (Irving et al., 1992). The dioptric differences in operating range can in part be attributed to absolute differences in eye size between chicks and monkeys. However, the relative changes in vitreous chamber depth that occur in response to imposed refractive errors in infant monkeys are also smaller than those in the chick. For example, the maximum lens-induced anisometropia in infant monkeys is associated with about a 1 mm interocular difference in vitreous chamber depth or about a 10% difference in vitreous chamber depth (Fig. 7). The vitreous chambers of monkeys that compensated for high-powered bilateral positive lenses also differ from those of monkeys that responded to high-powered negative lenses by about 1 mm (Fig. 11A). In comparison, the differences in vitreous chamber depth produced by high-powered negative and positive lenses (± 15 D) in the chick is also about 1 mm (Wildsoet & Wallman, 1995), however for the shorter chick vitreous chamber this represents about a 20% change in length.

It is reasonable to expect that the chick might exhibit a larger range of compensation, particularly for anisometropic lenses. Chicks exhibit a substantial amount of 'choroidal accommodation' (Wallman, Wildsoet, Xu, Gottlieb, Nickla, Marrian et al., 1995; Wildsoet & Wallman, 1995). Recent experiments in our lab show that, as in the chicken, the choroid in monkey eyes undergoes rapid compensating thickness changes in response to alterations in the eye's effective refractive status (Hung, Lin, Wallman & Smith, 1998). However, the extent of the choroid changes in the monkey eye are an order of magnitude smaller (e.g. about 30 vs. 300 microns) than those observed in the chicken (Wildsoet & Wallman, 1995). Chicks are also capable of high degrees of differential interocular accommodation (Schaeffel, Howland & Farkas, 1986; Schaeffel et al., 1988), whereas accommodation is more consensual in primates. Thus, while emmetropization is not entirely independent in the two eyes of either chicks (Wildsoet & Wallman, 1995) or monkeys (Hung et al., 1995), the two eyes of chicks are probably capable of functioning in a more independent manner. The preeminence of binocular vision in primates may also influence the range of compensation for both bilateral and anisometropic lenses. For example, constraints associated with the maintenance of binocular vision could influence lens compensation by limiting overall accommodative efforts and/or the monkey's general viewing pattern. In comparison to the chick, it is also likely that the monkey visual system is more susceptible to amblyopiogenic factors that could produce sensory deficits

that may interfere with compensating growth (Kiorpes & Wallman, 1995).

Although differences in eye size, maturational rates, ocular physiology and anatomy will undoubtedly influence the exact nature of the emmetropization response to a given change in the visual environment, the parallels between monkeys, chickens (Schaeffel et al., 1988; Irving et al., 1991; Irving et al., 1992; Wildsoet & Wallman, 1995), marmosets (Judge & Graham, 1995), tree shrews (Siegwart & Norton, 1993) and guinea pigs (McFadden & Wallman, 1995) are more striking than any observed differences. The cross species parallels argue that the vision-dependent mechanisms that mediate the effects of optical defocus on ocular growth are fundamental from an evolutionary point of view and that insights into emmetropization mechanisms obtained in one species are likely to apply to most species, including humans.

4.4. Relation to human refractive-error development

The phenomenon of emmetropization follows a qualitatively similar course in human and monkey infants. In both species, emmetropization occurs very quickly. Longitudinal human studies show that the large refractive errors that are frequently present at birth convergence toward a low degree of hyperopia very rapidly during the first year of life. By about 2 years of age the average spherical-equivalent refractive error for human infants becomes relatively stable near +1.0 D (Gwiazda, Thorn, Bauer & Held, 1993; Wood, Hodi & Morgan, 1995; Atkinson, Braddick, Bobier, Anker, Ehrlich, King et al., 1996). The bulk of the emmetropization process in infant monkeys is completed within the first 3–4 months of age and refractive error becomes relatively stable at moderate levels of hyperopia (about +2.5 D) by about 5–6 months of age. Thus, it appears that in monkeys the process of emmetropization takes place three to four times faster than in human infants. With the relatively small number of normal monkeys in the present study it is difficult to be more precise, however, this comparison is in good agreement with estimates of relative maturation rates obtained using other measures. Based on comparisons of the relative rates of axial elongation, Kiely et al. (1987) concluded that infant monkeys mature at a rate that was three times faster than that for human infants. Comparisons of a variety of visual functions have suggested that monkeys mature four times faster than humans (Boothe, Dobson & Teller, 1985).

In both humans and monkeys, emmetropization is largely completed by a given age regardless of the refractive error at or shortly after birth. As a result in both monkeys and humans (Saunders et al., 1995), the rate of refractive-error change during emmetropization is related to an individual's initial refractive error, the larger the initial refractive error the greater the rate of dioptric change. The rate differences between individuals do not reflect some innate interdependence between emmetropization rate and an individual's initial refractive error per se. Instead these rate differences apparently reflect the activity of vision-dependent mechanisms because the rate of compensation produced by spectacle lenses was also dependent on an animal's initial effective refractive error.

The gain of the emmetropization process in both monkeys and humans (Gwiazda et al., 1993) is less than one. As a consequence, an individual's relative position within the distribution of refractive errors does not change dramatically during maturation while the overall shape of the refractive-error distribution and the average refractive error do change. For example, neonates who have large initial effective hyperopic errors (either natural or imposed by spectacle lenses) will still tend to be more hyperopic once refractive status has stabilized later in infancy than neonates who were initially less hyperopic or myopic.

At the present time, there are not sufficient data available on human development to define the effective operating range of human emmetropization. However, with respect to anisometropic compensation, monkey and human infants appear to exhibit similar limitations. Recent longitudinal refractive data suggests that the eyes of human infants do not consistently grow in a manner that would eliminate anisometropias over about 3 D (Abrahamsson & Sjöstrand, 1996). Interestingly, like our infant monkeys that were fitted with 6 D anisometropic lenses, the non-fixating eyes of human infants who retained their anisometropia remained highly hyperopic despite the fact that the non-fixating eyes experienced high degrees of chronic defocus. Invariably these children with high degrees of persistent anisometropia also manifested amblyopia and/or strabismus (Abrahamsson & Sjöstrand, 1996). This observation is in agreement with the idea that sensory deficits may have interfered with emmetropization in some of our infant monkeys.

In light of the similarities between emmetropization in humans and monkeys, it is reasonable to expect that early in life visual feedback associated with an eye's effective refractive state also regulates human ocular growth. This raises the possibility that spectacle lenses prescribed for very young human infants could alter the normal emmetropization process. As an example, our results suggest that positive lenses prescribed for hyperopic infants very early during the first year of life would delay or reduce emmetropization. With respect to this issue, the existing human data, which are primarily from two longitudinal studies on the efficacy of positive spectacle lenses in reducing the incidence of binocular vision anomalies in at risk infants, are equivocal. Whereas Ingram, Arnold, Dally and Lucas (1991) re-

ported that hyperopic infants who were corrected with spectacle lenses were significantly less likely to exhibit a reduction in hyperopia than hyperopic infants who were not corrected with spectacles, Atkinson et al. (1996) did not find an overall difference in refractive development between uncorrected hyperopic infants and infants who wore partial optical corrections. A number of methodological concerns could potentially mask the effects of spectacle lenses on human emmetropization. Notably the onset age for lens wear in human infants is typically after the very early and most rapid period of emmetropization and it is likely that the inevitable interruptions in lens wear that occur with human infants could effectively eliminate the effects of lens wear. In this respect, it has been shown in chickens that very short periods of unrestricted vision can virtually eliminate the effects of a given experimental manipulation on refractive development (Napper et al., 1995; Schmid & Wildsoet, 1996). But it is also possible that the mechanisms that mediate emmetropization are not normal in infants who have high hyperopic errors early in life. For example if an infant was hyperopic because the eyes' emmetropization mechanism had an abnormally low gain, spectacle lenses would not be expected to affect refractive development. Obviously, it will be important to resolve these and a number of other issues before the experimental results from animals can be used to guide the clinical management of human refractive errors.

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